AMENDMENTS

Amendments to the Specification

1. Please replace the paragraph starting on page 1, ¶ 0001 with the following paragraph:

   The disclosures of ~~This application is a continuation-in-part of~~ U.S. Application Serial No. 10/757,077 ~~[Attorney Docket No. ALLE0014-103]~~ filed January 14, 2004, ~~which is a continuation-in-part of~~ U.S. Application Serial No. 10/163,106 filed June 4, 2002, ~~which is a continuation-in-part of~~ U.S. Application Serial No. 09/910,346 filed July 20, 2001 and ~~; which is a continuation-in-part~~ U.S. Patent No. 6,903,187 issued June 7, 2005 ~~Application Serial No. 09/620,840 filed July 21, 2000, the disclosures of which~~ are all incorporated herein by reference in their entirety.

2. Please replace the paragraph starting on page 25, ¶ 0097 with the following paragraph:

   A truncated form of LC/A (Tyr9-Leu415) has been reported as the minimal essential domain of the endoprotease, retaining a diminished catalytic activity towards SNAP25 (Kadkhodayan et al, 2000 , Protein Expr Purif 19, 125-30). The truncated LC/A structure (PDB structure #1E1H ~~- this structure is deposited in the database (see www.rcsb.org/pdb/ as of October 07, 2003~~) was reported to be similar to the LC/A structure in the holotoxin. A GFP fusion protein, GFP-LC/A (ΔN8ΔC22), containing the same truncations, was prepared and fluorescence imaging revealed the protein to no longer be localized to the plasma membrane. Instead, fluorescence appeared in perinuclear structures as well as throughout the cytoplasm (Figure 3A). These data suggest that signals involved in directing LC/A to the plasma membrane may reside within the deleted regions. Analysis of the primary sequence of LC/A using motif databases did reveal consensus sequences for common glycosylation and phosphorylation sites, in addition to the zinc-endopeptidase motif characteristic of Botulinum neurotoxins. Further analysis of the sequences revealed the presence of a putative di-Leucine motif (D/ExxxLL – SEQ ID NO:1) at the C-terminus of LC that was only present in the BoNT/A serotype (FEFYKLL - SEQ ID NO:2). Mutation of the

leucines into alanines, or mutation of the acidic residue (D/E -4 with respect to the first leucine) has been shown to disrupt the motif and thereby affect interaction with AP adaptors, protein internalization, and/or intracellular localization. 1E1H is the crystal structure of rLC/A(ΔN8/ΔC22). The peptide backbone of the crystal structure of this truncated form of rLC/A overlays very well on the backbone of LC/A in the holotoxin (150 kD - HC/LC) structure that is known. This suggests that the truncated LC is not substantially misfolded as a result of the truncation. It also suggests that LC structures do not change substantially once dissociated from the HC.